REMARKS

Restriction Requirement

The elected species read on claims 39, 43 45, 49 and 51 and these claims should not be withdrawn from consideration.

Information Disclosure statement

Copies of the foreign patent documents cited in the information disclosure statement of April 2, 2002 will be provided in a separate submission with a new 1449 form. Copies of the US patents will not been provided because the USPTO no longer requires their submission with an IDS. If the examiner does not have access to these patents, Applicants will provide copies.

Claim Objections and Rejection under 35 USC§ 112, second paragraph

The amendments to claims 1 and 7 address the objections made by the examiner and the rejection under 35 U.S.C. §112. These amendments do not change the scope of the claims.

Claim Rejections 35 USC 112

It is alleged that Claims 1, 3, 4 and 7-11 do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph.

The specification lists over two pages of publications which have linked TNFα production to a number of diseases including rheumatoid arthritis. The specification also lists a number of publications which have linked a number of diseases to excess metalloptrotease activity. The inhibition of p38 is known to inhibit TNFα production and MMP production such that p38 inhibitors are recognized to be useful in the treatment of these diseases. No evidence has been presented to the contrary.

It is alleged that Salituro et al (US 6,093,742) suggests the p38 inhibitory activity of a compound does not translate into in vivo efficacy at col 1, lines 54-58. Salituro et al clearly does not make such a suggestion by the statement at Col 1, lines 54-58 but instead refers to the need for additional p38 inhibitors. If the alleged suggestion were made, it would be inconsistent with the teachings of the reference. Salituro et al disclose and claim compounds said to be p38 inhibitors useful in treating

various conditions listed in column 40 lines 36 through column 41, line 42, without disclosing in vivo data.

No evidence has been presented and no scientific reasoning has been set forth as to why any of the compounds claimed would not be effective in treating the diseases specified, as is required to support a rejection under 35 USC § 112 , first paragraph. The specification provides adequate guidance as to how to make the active compounds by the generic and specific disclosure of synthesis methods and over 100 exemplified compounds. The specification also provides adequate disclosure as to how to use the compounds and provides dosage ranges for various methods of administration. Given the extent of the disclosure provided, it would at most involve routine experimentation if any at all, for one of ordinary skill in the art treat a p38 mediated disorder with a compound of this invention.

The compounds of formula are characterized by two features, (1) a bridged cyclic structure which is "A" of the formula $-L-(M-L^1)_q$ and (2) a required substituent on the cyclic structure L^1, selected from the group consisting of $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$. The specification provides ample guidance on how compounds with these features can be prepared, i.e., both broad teachings as well as specific reaction schemes to achieve the active compounds are provided. In addition, reference is made to other publications, i.e.,

March. *Advanced Organic Chemistry*, 3rd Ed.; John Wiley: New York (1985);

Larock. *Comprehensive Organic Transformations*; VCH Publishers: New York (1989);

Rylander. *Hydrogenation Methods*; Academic Press: London, UK (1985); and

(Seyden-Penne. *Reductions by the Alumino- and Borohydrides in Organic Synthesis*; VCH Publishers: New York (1991);

Furthermore, the specification teaches through examples how to prepare a large number of intermediates that provide the "A" groups and "B" groups of formula I , and also how to form ureas from these intermediates which allow for varying the identity of "B" and "the components of "A" , i.e., L and L^1. See specification page 25 to the end of page 62. This disclosure and the examples of this application are more than ample to provide enablement for compounds defined by the full scope of

formula I.

The specification also provides ample guidance as to how to prepare pharmaceutical compositions with the compounds of formula I and administer these compositions. See pages 16-21, line 2.

The Office Action nevertheless alleges that the specification lacks guidance for the treatment of diseases mediated by p38 using the compounds of formula I and lacks working examples relating to the treatment of the claimed diseases.

Even absent the disclosure and examples discussed above, which clearly meet the requirements of 35 U.S.C. § 112, first paragraph, the courts have placed the burden upon the PTO to provide evidence shedding doubt on the disclosure that the invention can be made and used as stated; see, e.g., *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971) (holding that how an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance.) The disclosure must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of the statement contained therein. See *In re Marzocchi*, supra. No such evidence or reason for doubting Applicants' disclosure is provided.

Additionally, "the [enablement] requirement is satisfied if, given what they [, those or ordinary skill in the art,] already know, the specification teaches those in the art enough that they can make and use the invention without 'undue experimentation.'" See *Amgen v Hoechst Marion Roussel*, 65 USPQ2d 1385 (CA FC 2003). Making the compounds of the claimed invention having the specific "A" and "B" groups of the claims, would be routine for those of ordinary skill in the art in view of applicant's disclosure. Explicitly providing examples for preparing species having each possible option for each "A" and "B" groups is not necessary to enable the same. See, for example, *Spectra-Physics v Coherent*, 827 F.2d 1524, 3 USPQ2d 1737 (Fed. Cir. 1987) ("A patent need not teach, and preferably omits, what is well known in the art"); *In re Howarth*, 654 F.2d at 105, 210 USPQ 689 (CCPA 1981) ("An inventor need not ... explain every detail since he is speaking to those skilled in the art."); *In re Gay*, 309 F.2d 769, 774, 135 USPQ 311 (CCPA 1962) ("Not every last detail is to be described, else patent specifications would turn into production specifications, which they were never intended to be.")

The specification, even though not necessary for an enabling disclosure, provides numerous, i.e., 100+ species of the claimed genus. There is no requirement that an applicant provide working examples for every species encompassed by the claims or to provide working examples relating to the treatment of the claimed diseases. See, for example, *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that applicants "are *not* required to disclose *every* species encompassed by their claims even in an unpredictable art"); *Utter v Higara*, 845 F.2d at 998-99, 6 USPQ2d 1714 (CAFC 1988) (holding that a specification may, within the meaning of Section 112, Para. 1, enable a broadly claimed invention without describing all species that claim encompasses). Instead, as discussed earlier, there is no requirement for any examples. See, for example, *Marzocchi*, supra, stating that "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The Examiner relies on In re Dreshfield 110 F2d. 235, 345 USPQ 36 (CCPA) as requiring the enumeration of "a sufficient number of examples" in cases involving "chemicals and chemical compounds which differ radically in their properties." The holding cited does not eliminate the need for evidence to support an enablement rejection under 112.

No evidence has been presented that the 100+ species of ureas provided (which vary in structure but for one of the required substituents and the bridged cyclic structure of "A") are insufficient . In addition, no evidence has been presented that any of the compounds of formula I vary radically in their properties.

The PTO has failed to meet its burden of establishing that the disclosure does not enable one skilled in the art to make the compounds recited in the claims. Instead of relying on proper probative evidence, the rejection is improperly based on the bare allegations. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the preparation of the claimed compounds without undue experimentation.

In addition, the Examiner's reliance on In re Dreshfield, 110 F.2d 235, 45 USPQ 36 (CCPA 1940) is misplaced. The court in Dreshfield did not address an enablement rejection of method of use claims, or as a matter of fact of any type of

claim. The claims involved were compound claims that were found to be broader than the original disclosure. See holding, i.e., "we are of the opinion that claims 15, 16, and 17 were properly rejected by the Primary Examiner on the ground that they are broader than appellant's original disclosure."

The Office Action lists several of the Wands factors and makes allegations with respect to these factors relating to the use of the compounds, but does not provide any factual basis for the allegations regarding these factors.

With respect to the predictability in the art, the Office Action alleges that the unpredictability in the art of steroids is very high. No support for this allegation is provided by the Office Action.

The Office Action further alleges that it would require a "case to case ... painstaking experimental study" to determine the activity levels of the claimed compounds. As discussed in Wands, supra, "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Here, the specification provides an assay and results on the activity of 100+ species. In a similar fashion, one of ordinary skill in the art by performing the same or similar tests, can, by routine experimentation, determine the activity levels of the remaining compounds of formula I.

Applicants provided adequate guidance and examples to the preparation of the compounds of formula I , have demonstrated that numerous representative species possess activity, and have provided guidance to those of ordinary skill in the art how to test the claimed compounds . Providing more is not necessary to enable the claimed invention.

As discussed above, the law does not require an applicant to test a compound in examples. See, for example, *Marzocchi*, supra, stating that whether "an enabling teaching is set forth, either by use of illustrative examples or by broad terminology, is of no importance." The MPEP also agrees by stating that "compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, does not turn on whether an example is disclosed." See MPEP § 2164.02.

The disclosure must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of

claim. The claims involved were compound claims that were found to be broader than the original disclosure. See holding, i.e., "we are of the opinion that claims 15, 16, and 17 were properly rejected by the Primary Examiner on the ground that they are broader than appellant's original disclosure."

The Office Action lists several of the Wands factors and makes allegations with respect to these factors relating to the use of the compounds, but does not provide any factual basis for the allegations regarding these factors.

With respect to the predictability in the art, the Office Action alleges that the unpredictability in the relevant art is very high. No support for this allegation is provided by the Office Action.

The Office Action further alleges that it would require a "case to case ... painstaking experimental study" to determine the activity levels of the claimed compounds. As discussed in Wands, supra, "considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." Here, the specification provides an assay and results on the activity of 100+ species. In a similar fashion, one of ordinary skill in the art by performing the same or similar tests, can, by routine experimentation, determine the activity levels of the remaining compounds of formula I.

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The disclosure must be taken as in compliance with the enabling requirement of the first paragraph of § 112 unless there is reason to doubt the objective truth of

the statement contained therein. See *In re Marzocchi*, supra. No reasons for such doubt have been provided.

With respect to pharmaceutical inventions, an applicant is not required to test the claimed compounds in their final use. The Federal Circuit in *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995), stated that

> usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful can be well before it is ready to be administered to humans. If the courts were to require Phase II testing in order to prove utility for pharmaceutical inventions, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas.

The specification of the application teaches that :

> Clinical studies have linked TNFα production and/or signaling to a number of diseases including rheumatoid arthritis (Maini. *J. Royal Coll. Physicians London* **1996**, *30*, 344). .... and
>
> Because inhibition of p38 leads to inhibition of TNFα production, p38 inhibitors will be useful in treatment of the above listed diseases.

Doubt has been held reasonable where, for example, the invention has been characterized as "highly unusual," *In re Houghton*, 433 F.2d 820 (CCPA 1970), as "incredible," *In re Citron*, 325 F.2d 248, (CCPA 1963), or as "too speculative," *In re Eltgroth*, 419 F.2d 918 (CCPA 1970). Because compounds having similar activities are known in the art, the existence of a new class of compounds having the claimed activities is not objectively doubtable, i.e., not "highly unusual," "incredible," and/or "too speculative."

Thus, the claimed methods of use are proper since the compounds were shown to possess the activity indicative of their usefulness in the claimed methods.

With regard to *Wands*, supra, used by the Examiner as the basis of the rejections, the court therein teaches that whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by

weighing many factual considerations. Factors to consider whether a disclosure requires undue experimentation are summarized to include the 8 *Wands* factors (not reproduced here). No factor alone is determinative. The court in *Wands*, further held that the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

Instead of relying on proper probative evidence, the rejection is improperly based on bare allegations and unsupported conclusions about the adequacy of the disclosure. No evidence has been presented which would demonstrate that the guidance provided by the specification is inadequate to enable the preparation and use of the claimed compounds without undue experimentation.

Applicants provide numerous examples and ample direction in the specification with respect to the direction in which experimentation should proceed, for example:

- provide 100+ exemplified species,
- test each of these compounds in an *in vitro* p38 kinase assay and demonstrates activity in all the compounds by providing IC_{50} data, (see page 101),
- teaches the method of testing the inhibitory effect of the compounds in an *in vivo* assay, (see page 101),

Applicants provide ample evidence to the claimed activity and ample guidance to test the activity of further compounds according to the invention. Any one of the claimed compounds can be tested by routine protocol known to those of ordinary skill in the art. As stated by the court in *Wands*, supra, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

For the reasons discussed above, Applicants submit that claims 1, 3, 4, 7-11 meet the requirements of 35 USC § 112 , first paragraph.

Rejection Under 35 USC 103

Claims 1, 3, 4 and 7-11 are rejected under 35 U,S.C. § 103 based on Salituro

et al. (US 6,093,742). The teachings of Salituro et al. provide no hint or suggestion to either:

(1) incorporate a substituent at the position required of the urea compounds claimed herein (L^1 of --L-$(M\text{-}L^1)_q$, or

(2) incorporate one of the required substituents on the urea compounds claimed herein($-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)\ R_z$) at this position.

The urea compounds claimed herein require one of the following three substituents, $-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)\ R_z$, on cyclic group "L^1" of the moiety "A" which is of the formula $-L(M\text{-}L^1)_q$. Cyclic group "L^1" is bound to cyclic structure 'L" through a bridging group "M". Cyclic structure "L" is bound directly to a urea group.

The broad disclosure of Salituro et al. encompasses urea compounds with a bridged structure that conforms to "A" ($-L(M\text{-}L^1)_q$) herein. This occurs where R^1 is $-OR^3$, $-N(R^3)_2$, $-CO_2R^3$, $-CON(R^3)$, $-NHCOR^3$, $-SO_2NR^3$ and SR^3 and R^3 is C_6-C_{20} aryl.

Salituro et al provide some examples of ureas with bridged cyclic structures which are compound numbers: 20, 21, 23, 36, 52, 53, 54, 55 and 123. Not one of these compounds has a substituent on the remote cyclic structure that conforms to L^1 of "A" ($-L(M\text{-}L^1)_q$.

The broad disclosure of Salituro also provides no direction to incorporate a substituent on a remote cyclic ring that conforms to L^1 of a urea. The broad disclosure at col. 2 lines 15-40 indicates substituents can appear on R^3 ; however R^3 can be many things other than a cyclic structure and the compounds of formula I of Salituro et al. encompass many compounds other than ureas.

In that there is no direction from the broad or specific teachings of Salituro et al. to substitute the remote cyclic ring of a urea compound, there is clearly no direction to select any of the required substituents ($-SO_2R_x$, $-C(O)R_x$ and $-C(NR_y)R_z$) that appear on the ureas employed in the present invention and therefore, the compounds and the methods claimed herein are unobvious.

Incorporating these substituents is a significant deviation in structure from the compounds of Salituro et al. To select all of the variables necessary to arrive at the ureas of this invention, it is necessary to rely on the applicants claim as a blueprint, which is improper. *Interconnect Planning Corp. v. Feil,* 774 F2. 1132, 227 USPQ 543 (Fed.Cir.1985).

Based on the above remarks, Applicants submit that withdrawn claims 39, 43 45, 49 and 51 should be examined and that claims 1, 3, 4 and 7-11 and withdrawn claims 39, 43 45, 49 and 51 are in a form suitable for allowance and patentable over the cited reference. Therefore, withdrawal of the rejections and allowance of these claims are earnestly solicited.

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